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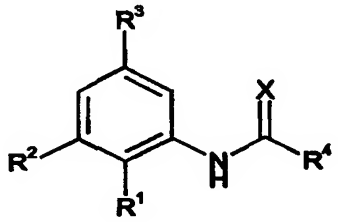
(54) Title: DERIVATIVES OF 2,5– AND 3,5–DISUBSTITUTED ANILINES, THEIR PREPARATION AND USE

(57) Abstract

Substituted anilines of general formula (I) wherein $R^1$, $R^2$, $R^3$, $R^4$ and X are defined in the description, compositions thereof and methods for preparing the compounds are described. The compounds are useful for the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the urogenital system, the gastrointestinal system and the endocrinological system.

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# Derivatives of 2,5- and 3,5-disubstituted anilines, their Preparation and Use

## FIELD OF THE INVENTION

The present invention relates to derivatives of 2,5- and 3,5-disubstituted anilines, to methods for their preparation, to compositions comprising these compounds, to the use of these compounds as medicaments and their use in therapy e.g. in the treatment of diseases of the central nervous system, the cardiovascular system, the pulmonary system, the urogenital system, the gastrointestinal system and the endocrinological system.

## BACKGROUND OF THE INVENTION

Potassium channels play an important role in the physiological and pharmacological control of cellular membrane potential. Amongst the different types of potassium channels are the ATP-sensitive ($K_{ATP}$-) channels which are regulated by changes in the intracellular concentration of adenosine triphosphate. The $K_{ATP}$-channels have been found in cells from various tissues such as cardiac cells, pancreatic cells, skeletal muscles, smooth muscles, central neurones and adenohypophysis cells. The channels have been associated with diverse cellular functions, as for example hormone secretion (insulin from pancreatic beta-cells, growth hormone and prolactin from adenohypophysis cells), vasodilation (in smooth muscle cells), cardiac action potential duration and neurotransmitter release in the central nervous system.

Modulators of the $K_{ATP}$-channels have been found to be of importance for the treatment of various diseases. Certain sulfonylureas which have been used for the treatment of non-insulin-dependent diabetes mellitus act by stimulating insulin release through an inhibition of the $K_{ATP}$ -channels on pancreatic beta-cells.

The potassium channel openers, which comprise a heterogeneous group of compounds, have been found to be able to relax vascular smooth muscles and have therefore been used for the treatment of hypertension.

In addition, potassium channel openers can be used as bronchodilators in the treatment of asthma and various other diseases.

Furthermore, potassium channel openers have been shown to promote hair growth, and have been used for the treatment of baldness.

Potassium channel openers are also able to relax urinary bladder smooth muscle and can therefore be used for the treatment of urinary incontinence. Potassium channel openers which relax smooth muscle of the uterus can be used for treatment of premature labour.

Since some $K_{ATP}$-openers are able to antagonize vasospasms in basilar or cerebral arteries the compounds of the present invention can be used for the treatment of vasospastic disorders such as subarachnoid haemorrhage and migraine.

Potassium channel openers hyperpolarize neurons and inhibit neurotransmitter release, and therefore the present compounds may be useful for the treatment of various diseases of the central nervous system, e.g. epilepsia, ischemia and neurodegenerative diseases, and for the treatment of pain.

Recently it has been shown that diazoxide (7-chloro-3-methyl-2H-1,2,4-benzothiadiazine 1,1-dioxide) and certain 3-(alkylamino)-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide derivatives inhibit insulin release by an activation of $K_{ATP}$-channels on pancreatic beta-cells (Pirotte B. et al., *Biochem. Pharmacol.* **1994**, *47*, 1381-1386; Pirotte B. et al., *J. Med. Chem.* **1993**, *36*, 3211-3213. Diazoxide has furthermore been shown to delay the onset of diabetes in BB-rats ( Vlahos W.D. et al., *Metabolism* **1991**, *40*, 39-46. In obese Zucker rats diazoxide has been shown to decrease insulin secretion and increase insulin receptor binding and consequently improve glucose tolerance and decrease weight gain (Alemzadeh R. et al., *Endocrinol.* **1993**, *133*, 705-712). It is expected that such potassium channel openers can be used for treatment of diseases characterized by an overproduction of insulin and for the treatment and prevention of diabetes.

Derivatives of 3,5-bis(trifluoromethyl)aniline, 3,5-dichloroaniline, 2,5-bis(trifluoromethyl)aniline and other, similarly substituted anilines have been previously

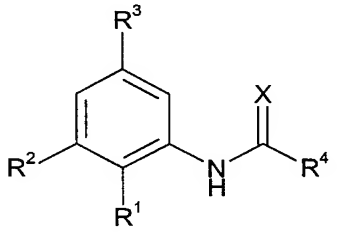
claimed as crop protecting agents, antibacterials, anti-snails and for other uses, but not as potassium channel openers:

FR 1507886, Chem. Abstr., 70, 19821k, 1969; Agfa A.G., DE 1116534, 1961, Chem. Abstr., EN, 56, 10329h, 1962; Ciba-Geigy AG, Basel (Schweiz), DE 2617163, 1976, Chem. Abstr., EN, 86, 55279; Hoechst, DE 2546271, 1977, Chem. Abstr., EN, 87, 64057; Dow Chemical Co., US 3755505, 1970, Chem. Abstr., EN, 79, 104972; Ciba, NL 6516437, 1966, Chem. Abstr., EN, 66, 2329j, 1967; CIBA Ltd., FR 1511325, 1966, Chem. Abstr., EN, 71, 91052y, 1969; CIBA, CH 495703, 1970, Chem. Abstr., EN, 74, 79613; Ciba, US 3592932, 1971; CIBA Ltd., DE 1803084, 1967, Chem. Abstr., EN, 71, 91119a, 1969; Bayer AG, DE 2623847, 1977, Chem. Abstr., EN, 88, 120822; Labor.J.Berthier S.A., ZA 6706114, 1968, Chem. Abstr., EN, 70, 57467g, 1969.

Amides from 3,5-dichloroaniline and linear aliphatic carboxylic acids have been described as antibacterials (*J. Med. Chem.* **1983**, *26*, 1741).

## DESCRIPTION OF THE INVENTION

The present invention relates to derivatives of 2,5- and 3,5-bis-substituted anilines of the general formula I:



I

wherein

$R^1$ is hydrogen, trifluoromethyl or halogen;

$R^2$ is hydrogen, trifluoromethyl or halogen;

$R^3$ is trifluoromethyl or halogen;

$R^4$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl or aryloxy; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or

aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

Y-$R^5$, wherein Y is -O- or -N($R^6$)-

wherein $R^5$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl;

heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or

aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;

$R^6$ is hydrogen; or

straight or branched alkyl optionally substituted with $C_{3-8}$-cycloalkyl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or

aryloxy optionally substituted with halogen, cyano or trifluoromethyl;; or

$R^5$ and $R^6$ are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl or pyrrolidinylcarbonylmethyl; or

aryl optionally substituted with halogen, cyano or trifluoromethyl; or

furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or

piperidinyl; or

$R^5$ and $R^6$ are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that $R^1$ and $R^2$ are not both hydrogen at the same time;

and further provided that when $R^2$ is hydrogen and $R^1$ and $R^3$ are chloro, then

$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
$R^4$ can not be n-alkyl;
$R^4$ can not be $-(CH_2)_3$-OAr;
$R^4$ can not be 2,6-dimethylpiperidin-1-yl, methylamino, butylamino, benzylamino, arylamino, dimethylamino, diethylamino, dipropylamino, dibenzylamino, (methyl)(propargyl)amino, (1-phenylcyclohex-1-yl)methylamino, 4-heteroarylpiperazin-1-yl, (6-methylpyridin-2-yl)methylamino, (4-pyridinylmethyl)(methyl)amino or 2,5-dimethylpyrrolidin-1-yl.

When $R^2$ is hydrogen and $R^1$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be methyl, pyridyl, ethyl, n-propyl or 2-propylbutyl.

When $R^1$ is hydrogen and $R^2$ and $R^3$ are chloro, then
$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
$R^4$ can not be n-alkyl, cyclopropyl or 2-propylbutyl;
$R^4$ can not be $-(CH_2)_3$-OAr or $-CH(OH)CH_3$;
$R^4$ can not be arylamino, methylamino, isobutylamino, butylamino, 3-hydroxypropylamino, dimethylamino, [1-methyl-1-(4-bromophenyl)ethyl]amino, (methyl)(propargyl)amino, (isopropyl)(propargyl)amino, di(n-butyl)amino, dibenzylamino or (benzyl)(n-butyl)amino.

When X is oxygen, $R^1$ is hydrogen and $R^2$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with heteroaryloxy, ammonium, acyl, 1-oximoalkyl, heterocyclyl or 1-iminoalkyl;
$R^4$ can not be 2-propylbutyl or cyclopropyl;
$R^4$ can not be benzylamino, 2-phenylethylamino, (1-phenyl)ethylamino, 4-chlorobenzylamino, 2-chlorobenzylamino, 2-(4-chlorophenyl)ethylamino, 3,4-dichlorobenzylamino, (3,4-dichlorobenzyl)(methyl)amino, (2-ethylhex-1-yl)amino, isopropylamino, propylamino, butylamino or 4-methyl-1-piperazinyl.

When X is sulfur, $R^1$ is hydrogen and $R^2$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be benzylamino, 3,4-dimethylbenzylamino, 4-methoxybenzylamino, 3,4-dichlorobenzylamino, (2-hydroxy-1-methyl-2-phenylethyl)(methyl)amino, isopropylamino, n-propylamino, n-pentylamino, 4-chlorobenzylamino, 1-piperidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, 2,6-dimethyl-4-thiomorpholinyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl or 4-ethoxycarbonylpiperazin-1-yl;

When $R^1$ is chloro, $R^2$ is hydrogen and $R^3$ is trifluoromethyl, then
$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or substituted with aryl, heteroaryl, aryloxy, amino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium, aminoalkyl;
$R^4$ can not be unsubstituted n-alkyl, cyclopropyl, isopropyl, isobutyl, benzyl, 2-ethylpropyl, 2-propylbutyl;
$R^4$ can not be diisopropylamino, 2,6-dimethylpiperidin-1-yl, methylamino, dimethylamino, (1,1-dimethylpropargyl)amino, ethylamino, butylamino, (2-hydroxyprop-1-yl)amino or 1-adamantylamino.

Within its scope the invention includes all diastereomers and enantiomers of compounds of formula I, some of which are optically active, and also their mixtures including racemic mixtures thereof.

The scope of the invention also includes all tautomeric forms of the compounds of formula I.

The salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable metal salts or optionally alkylated ammonium salts, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, trifluoroacetic, trichloroacetic, oxalic, maleic, pyruvic, malonic, succinic, citric, tartaric, fumaric, mandelic, benzoic, cinnamic, methanesulfonic, ethanesulfonic, picric and the like, and include acids related to the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, 2, and incorporated herein by reference, or lithium, sodium, potassium, magnesium and the like.

The term "heterocyclyl" as used herein refers to: a monocyclic unsaturated or saturated system containing one, two or three hetero atoms selected from nitrogen, oxygen and sulfur and having 5 members, e.g. a radical derived from pyrrole, furan, thiophene, pyrroline, dihydrofuran, dihydrothiophene, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, thiazole, isoxazole, isothiazole, 1,2,3-oxadiazole, furazan, 1,2,3-triazole, 1,2,3-thiadiazole or 2,1,3-thiadiazole; an aromatic monocyclic system containing two or more nitrogen atoms and having 6 members, e.g. a radical derived from pyrazine, pyrimidine, pyridazine, 1,2,4-triazine, 1,2,3-triazine or tetrazine; a non-aromatic monocyclic system containing one or more hetero atoms selected from nitrogen, oxygen and sulfur and having 6 or 7 members, e.g. a radical derived from pyran, thiopyran, piperidine, dioxane, oxazine, isoxazine, dithiane, oxathine, thiazine, piperazine, thiadiazine, dithiazine, oxadiazine or oxoazepane as well as the corresponding benzo and dibenzo derivatives.

Alkyl refers to lower straight, cyclic, bicyclic, fused or branched alkyl having 1 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Aryl refers to phenyl or phenyl substituted with alkyl or phenyl, or phenyl fused with cycloalkyl, or polycyclic aromatic systems such as naphthyl, anthracenyl, phenanthrenyl, fluorenyl, etc. Alkylene refers to lower straight, cyclic, fused or branched alkylene having 1 to 15 carbon atoms, preferentially 1 to 6 carbon atoms. Heteroaryl refers to any of the possible isomeric, unsubstituted or alkyl-substituted pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, thiazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl and pyridazinyl, as well as the corresponding benzo and dibenzo derivatives or other fused ring-systems thereof. Heteroaryl is also intended to mean the partially or fully hydrogenated derivatives of the heterocyclic systems enumerated above. Alkoxy refers to -O-alkyl and aryloxy refers to -O-aryl. Cyano refers to -CN, hydroxy refers to -OH, amino refers to $-NH_2$ and nitro refers to $-NO_2$. Dialkylamino refers to $-N(alkyl)_2$. Alkylarylamino refers to -N(alkyl)(aryl) and diarylamino refers to $-N(aryl)_2$. Halogen refers to -F, -Cl, -Br and -I. Aralkyl refers to -alkylene-aryl. Alkylthio refers to -S-alkyl and arylthio refers to -S-aryl. Alkoxycarbonyl refers to -CO-O-alkyl and aminocarbonyl refers to $-CO-NH_2$, -CONH(alkyl), -CONH(aryl), $-CO-N(alkyl)_2$, -CO-N(alkyl)(aryl) or $-CO-N(aryl)_2$. Acylamino refers to -NH-CO-(alkyl), -NH-CO-(aryl), -N(alkyl)-CO-alkyl or -N(alkyl)-CO-aryl. A leaving group refers to a group or atom capable of existing in solution as a negatively charged species, or a positively charged group or atom.

The term "$C_{2-6}$-alkenyl" as used herein refers to an unsaturated hydrocarbon chain having 2-6 carbon atoms and one double bond such as e.g. vinyl, 1-propenyl, allyl, isopropenyl, n-butenyl, n-pentenyl and n-hexenyl.

The term "$C_{2-6}$-alkynyl" as used herein refers to unsaturated hydrocarbons which contain triple bonds, such as e.g. $-C\equiv CH$, $-C\equiv CCH_3$, $-CH_2C\equiv CH$, $-CH_2CH_2C\equiv CH$, $-CH(CH_3)C\equiv CH$, and the like.

The compounds of the present invention interact with the potassium channels and hence act as openers or blockers of the ATP-regulated potassium channels, making them potentially useful for the treatment of various diseases of the cardiovascular system, e.g. cerebral ischemia, hypertension, ischemic heart diseases, angina pectoris and coronary heart diseases; the pulmonary system; the urogenital system; the gastrointestinal system; the central nervous system and the endocrinological system.

The compounds of the present invention may also be used for the treatment of diseases associated with decreased skeletal muscle blood flow such as Reynauds disease and intermittent claudication.

Further, the compounds of the invention may be used for the treatment of chronic airway diseases, including asthma, and for treatment of detrusor muscle instability secondary to bladder outflow obstruction and therefore for kidney stones by aiding their passage along the ureter. Potassium channel openers also relax urinary bladder smooth muscle, thus, the compounds of the present invention can be used for the treatment of urinary incontinence.

The present compounds could also be used for treatment of conditions associated with disturbances in gastrointestinal mobility such as irritable bowel syndrome. Additionally these compounds can be used for the treatment of premature labor and dysmenorrhea.

Further, potassium channel openers promote hairgrowth, therefore, the compounds of the present invention can be used for the treatment of baldness.

In diseases such as nesidioblastosis and insulinoma in which a hypersecretion of insulin causes severe hypoglycemia the compounds of the present invention may be used to reduce insulin secretion. In obesity hyperinsulinemia and insulin resistance is very frequently encountered. This condition could lead to the development of non insulin dependent diabetes (NIDDM). Potassium channel openers and hence the compounds of the present invention may be used for counteracting the hyperinsulinemia and thereby prevent diabetes and reduce obesity. In overt NIDDM treatment of hyperinsulinemia with potassium channel openers, and hence the present compounds, can be of benefit in restoring glucose sensitivity and normal insulin secretions.

In early cases of insulin dependent diabetes (IDDM) or in prediabetic cases, potassium channel openers and hence the present compounds may be used to induce beta-cell rest which may prevent the progression of the autoimmune disease. The title compounds may be used to reduce beta-cell degeneration in type 1 or type 2 diabetes and to normalize insulin secretion and improve insulin resistance in type 2 diabetes.

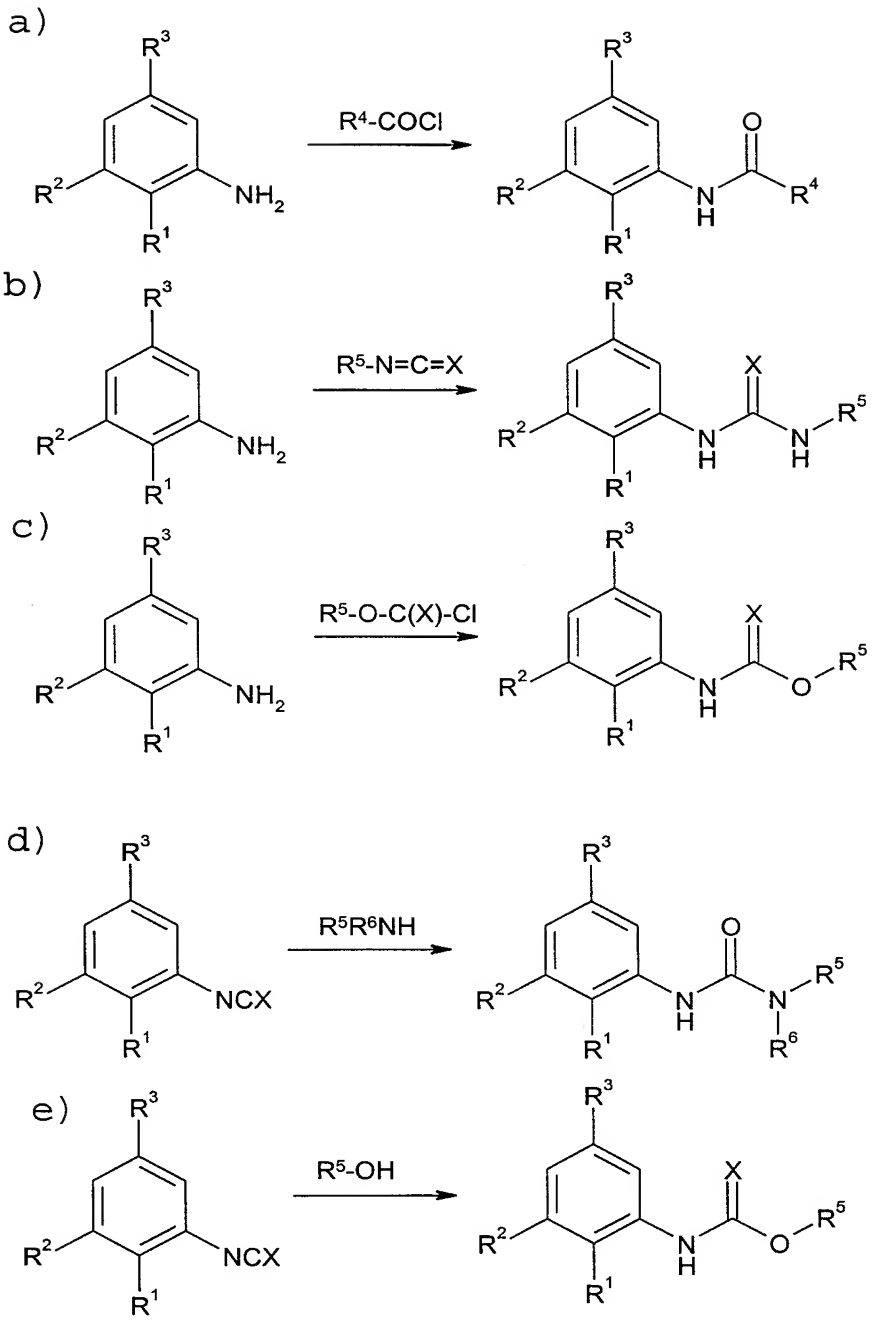
Compounds of the present invention which act as blockers of $K_{ATP}$-channels may be used for the treatment of NIDDM.

Preferably, the compounds of the present invention may be used for treatment or prevention of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

Accordingly, in another aspect the invention relates to a compound of the general formula I or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of hyperinsulinaemia and treatment or prevention of diabetes.

Furthermore, the invention also relates to the use of the inventive compounds of formula I as medicaments useful for treating hyperinsulinaemia and treating or preventing diabetes .

The compounds of this invention can be prepared by many different routes, obvious to those skilled in the art. Some of these routes are sketched below




Substituted anilines can be e.g. reacted with the appropriate carboxylic acid chlorides to yield anilides. Moreover, reaction with isocyanates of isothiocyanates may give ureas or thioureas, respectively. Reaction of substituted anilines with chloroformates may yield carbamates (urethanes).

Moreover, substituted arylisocyanates (X = O) or arylisothiocyanates (X = S) may be reacted with primary or secondary aliphatic or aromatic amines to yield ureas or thioureas, respec-

tively. Substituted arylisocyanates (X = O) or arylisothiocyanates (X = S) may also be reacted with aliphatic or aromatic alcohols to yield urethanes (carbamates) or thiocarbamates.

7. Abbreviations: The following frequently used abbreviations are intended to have the following meanings:

AcOH: glacial acetic acid

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCM: dichloromethane, methylenechloride

DIC: diisopropylcarbodiimide

DMF: N,N-dimethyl formamide

EDC: N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride, "water-soluble carbodiimide"

FMoc: fluorenylmethyloxycarbonyl

NMP: N-Methylpyrrolidone

R: organic radical

TFA: trifluoroacetic acid

THF: tetrahydrofuran

PHARMACOLOGICAL METHODS

The ability of the compounds to interact with potassium channels can be determined by various methods. When patch-clamp techniques (Hamill O.P., Marty A., Nefer E., Sakman B. and Sigworth F.J., *Plügers Arch.* **1981**, *391*, 85-100) are used the ionic current through a single channel of a cell can be recorded.

The activity of the compounds as potassium channel openers can also be measured as relaxation of rat aorta rings according to the following procedure:

A section of rat thoracic aorta between the aortic arch and the diaphragm was dissected out and mounted as ring preparations as described by Taylor P.D. et al., *Brit. J. Pharmacol.* **1994**, *111*, 42-48.

After a 45 min equilibration period under a tension of 2 g, the preparations were contracted to achieve 80% of the maximum response using the required concentration of

phenylephrine. When the phenylephrine response reached a plateau, potential vasodilatory agents were added cumulatively to the bath in small volumes using half log molar increments at 2 min intervals. Relaxation was expressed at the percentage of the contracted tension. The potency of a compound was expressed as the concentration required to evoke a 50% relaxation of the tissue.

In the pancreatic beta-cell the opening of the $K_{ATP}$-channels can be determined by measuring the subsequent change in the concentration of cytoplasmic free $Ca^{2+}$ concentration according to the method of Arkhammar et al., *J. Biol. Chem.* **1987**, *262*, 5448-5454.

$^{86}Rb^+$ efflux from a beta-cell line

The RIN 5F cell line was grown in RPMI 1640 with Glutamax I, supplemented with 10% fetal calf serum (from GibcoBRL, Scotland, UK) and maintained in an atmosphere of 5% $CO_2$/ 95% air at 37 °C. The cells were detached with a Trypsin-EDTA solution (from GibcoBRL, Scotland, UK), resuspended in medium, added 1 mCi/mL $^{86}Rb^+$ and replated into microtiter plates (96 well cluster 3596, sterile, from Costar Corporation, MA, USA) at a density of 50000 cells/well in 100 µl/well, and grown 24 hours before use in assay.

The plates were washed four times with Ringer buffer (150 mM NaCl, 10 mM Hepes, 3.0 mM KCl, 1.0 mM $CaCl_2$, 20 mM sucrose, pH 7.1). 80 µL Ringer buffer and 1 µL control- or test compound dissolved in DMSO were added. After incubation for 1 h at room temperature with a lid, 50 µL of the supernatant was transferred to PicoPlates (Packard Instrument Company, CT, USA) and 100 µL MicroScint40 (Packard Instrument Company, CT, USA) was added. The plates were counted in TopCount (Packard Instrument Company, CT, USA) for 1 min/well at the $^{32}P$ program.

The calculation of $EC_{50}$ and $E_{max}$ was done by SlideWrite (Advanced Graphics Software, Inc., CA, USA) using a four parameter logistic curve: $y = (a-d)/(1+(x/c)^b)+d$, where a = the activity estimated at concentration zero, b = a slope factor, c = the concentration at the middle of the curve and, d = the activity estimated at infinite concentration. $EC_{50}$ = c and $E_{max}$ = d, when the curve is turned off at infinite concentrations.

The compounds according to the invention are effective over a wide dose range. In general satisfactory results are obtained with dosages from about 0.05 mg to about 1000 mg, preferably from about 0.1 mg to about 500 mg, per day. A most preferable dosage is about 5 mg to about 200 mg per day. The exact dosage will depend upon the mode of administration, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral or parenteral e.g. rectal, transdermal, subcutaneous, intravenous, intramuscular or intranasal, the oral route being preferred.

Typical compositions include a compound of formula I or a pharmaceutically acceptable salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet, appropriate for use in this method, may be prepared by conventional tabletting techniques and contains:

| | |
|---|---|
| Active compound | 5.0 mg |
| Lactosum | 67.8 mg Ph.Eur. |
| Avicel® | 31.4 mg |
| Amberlite® | 1.0 mg |
| Magnesii stearas | 0.25 mg Ph.Eur. |

Due to their high degree of activity, the compounds of the invention may be administered to a mammal, especially a human, in need of such treatment, prevention, elimination, alleviation or amelioration of various diseases as mentioned above and especially of diseases of the endocrinological system such as hyperinsulinaemia and diabetes.

The results obtained from screening of the compounds of the present invention show, that some of these are potent potassium channel openers. The most active compounds of this invention show an $IC_{50}$ of 600 nM.

**Examples**

*Example 1. 1-[3,5-Bis-(trifluoromethyl)phenyl]-3-(2,4-dichlorobenzyl)urea*

To a solution of 2,4-dichlorobenzylisocyanate (0.22 g, 1.09 mmol) in toluene (4.5 mL) 3,5-bis(trifluoromethyl)aniline (0.16 mL, 1.03 mmol) and triethylamine (0.3 mL) were added and the resulting mixture was heated to 90 °C for 2 h. The mixture was then concentrated and

the residue recrystallized from ethyl acetate (10 mL). 0.15 g (34%) of the title compound was obtained as colourless needles, mp 196-198 °C.

HPLC (254 nm): Elution at 33.98 min, 99.7% pure. LCMS: $MH^+$ calcd.: 431, found: 431. $^1H$ NMR (300 MHz, DMSO-$d_6$): $\delta$ = 4.38 (d, $J$ = 7 Hz, 2H), 7.09 (t, $J$ = 7 Hz, 1H), 7.30-7.62 (m, 6H), 8.11 (s, 2H), 9.52 (s, 1H). Anal. Calcd. for $C_{16}H_{10}Cl_2F_6N_2O$ (431.2): C, 44.57; H, 2.34; N, 6.50. Found: C, 44.53; H, 2.34; N, 6.29.

*Example 2. Parallel Synthesis of ten N-acylated 3,5-bis(trifluoromethyl)anilines*

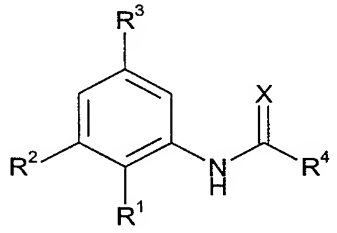
Into each of ten test tubes with septum a solution of 3,5-bis(trifluoromethyl)aniline (0.078 mL, 0.5 mmol) in pyridine (0.2 mL) and 1,2-dichloroethane (0.5 mL) was placed. Then, while shaking the tubes on a mechanical shaker, to each of the test tubes one acid chloride (0.6 mmol), namely 3-cyanobenzoyl chloride, 2-phenoxypropionyl chloride, butyryl chloride, heptanoyl chloride, pivaloyl chloride, cyclopropanoyl chloride, isobutyryl chloride, 2-ethylhexanoyl chloride, 3-cyclopentylpropionyl chloride and 3-phenylpropionyl chloride, was added with a syringe. The resulting mixtures were shaken for 48 h at room temperature. To each test tube brine (2 mL) and ethyl acetate (2 mL) were added, and after shaking for 5 min the aqueous phases were pipetted off and discarded. The organic layers were washed once with 1N hydrochloric acid (3 mL), once with brine (3 mL) and then dried over magnesium sulfate. The dried ethyl acetate extracts were tranferred into vials and concentrated. Between 156 mg and 63 mg of the corresponding anilides were obtained. Purity and identity of the products was determined by HPLC-MS, and was found to be sufficient for screening.

*Example 3. Parallel synthesis of 200 substituted aniline derivatives*

An array of 200 different aniline derivatives was prepared in the following way:
Into 200 vials 0.1 mmol of 50 different amines was placed. The amines were: isoamylamine, isopropylamine, isobutylamine, neopentylamine, 2,2,2-trifluoroethylamine, propargylamine, dipropylamine, 2-(4-chlorophenyl)ethylamine, 4-methylpiperidine, diisobutylamine, pyrrolidine, 3-(imidazol-1-yl)propylamine, 1,2,3,4-tetrahydroisoquinoline, cis-2,6-dimethylmorpholine, 1-[(3-trifluoromethyl)phenyl]piperazine, azepine, 4-benzoylpiperidine, (3-phenylpropyl)amine, 4-hydroxycyclohexylamine (cis/trans-mixture), trans-3-hydroxycyclohexylamine, 3-hydroxypiperidine, 3-hydroxypyrrolidine, 2-aminoethanol, 3-

aminopropanol, 4-aminobutanol, 6-aminohexanol, 4-(2-aminoethyl)morpholine, 3,3,5-trimethyl-5-aminomethyl-1-cyclohexanol, 1-acetylpiperazine, (2-chlorobenzyl)amine, 2-(ethylamino)ethanol, n-butylamine, 2-methyl-2-amino-1-propanol, cyclohexylmethylamine, 4-(2-aminoethyl)pyridine, 4-(ethylaminomethyl)pyridine, 3-(2-pyridylamino)propylamine, 2-(2-aminoethyl)pyridine, 4-(1-piperidinyl)-4-(aminocarbonyl)piperidine, 1-(pyrrolidin-1-ylcarbonylmethyl)piperazine, 1-(2-furoyl)piperazine, 1-cyclopropyl-1-(4-methoxyphenyl)methylamine, synephrine [N-methyl-2-(4-hydroxyphenyl)-2-hydroxyethylamine; racemic], 2-amino-2-phenylethanol (racemic), norephedrine (1-phenyl-2-aminopropanol), 4-amino-1-benzylpiperidine, 1,2,3,4-tetrahydropapaverine, desipramine and 3-(aminomethyl)pyridine. Then to each of the vials (closed with a septum) 0.25 mL of a mixture of acetonitrile and triethylamine (9:1, vol) was added. Finally solutions of 3,5-bis(trifluoromethyl)phenylisothiocyanate, 3,5-dichlorophenylisothiocyanate, 3,5-bis(trifluoromethyl)phenylisocyanate and 2-chloro-5-(trifluoromethyl)phenylisothiocyanate in acetonitrile (0.6 equivalents) were added to all the vials in such a way that all possible combinations of cyanate/amine were realized. The vials were then shaken for 24 h at room temperature and then concentrated in vacuum. The quality of the compound-array was determined by HPLC-MS of a representative selection of products, and was considered to be sufficient for screening (estimated purity of analyzed samples: 40% to >90%).

Following the procedures described above, the following compounds **I** have been prepared:



**I**

| No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X | $MH^+$ expctd | $MH^+$ found |
|---|---|---|---|---|---|---|---|
| 1 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2CH_3$ | O | 315 | 315 |
| 2 | H | $-CF_3$ | $-CF_3$ | -NH-(cyclohexyl) | O | 355 | 355 |
| 3 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_3$ | O | 328 | 329 |
| 4 | H | $-CF_3$ | $-CF_3$ | $-NH-(4-C_6H_4Cl)$ | O | 383 | 383 |
| 5 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)_2$ | O | 315 | 315 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 6 | H | $-CF_3$ | $-CF_3$ | $-(3-C_6H_4CN)$ | O | 359 | 359 |
| 7 | H | $-CF_3$ | $-CF_3$ | $-CH(O-Ph)CH_3$ | O | 378 | 378 |
| 8 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2CH_3$ | O | 300 | 300 |
| 9 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_5CH_3$ | O | 342 | 342 |
| 10 | H | $-CF_3$ | $-CF_3$ | $-C(CH_3)_3$ | O | 314 | 314 |
| 11 | H | $-CF_3$ | $-CF_3$ | cyclopropyl | O | 298 | 298 |
| 12 | H | $-CF_3$ | $-CF_3$ | $-CH(CH_3)_2$ | O | 300 | |
| 13 | H | $-CF_3$ | $-CF_3$ | -CH(Et)(n-butyl) | O | 356 | 356 |
| 14 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2$-(cyclopentyl) | O | 354 | 354 |
| 15 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2$-Ph | O | 362 | 362 |
| 16 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-CH(CH_3)_2$ | S | 359 | |
| 17 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)_2$ | S | 331 | 331 |
| 18 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CH(CH_3)_2$ | S | 345 | |
| 19 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-C(CH_3)_3$ | S | 359 | 359 |
| 20 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CF_3$ | S | 371 | |
| 21 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CCH$ | S | 327 | |
| 22 | H | $-CF_3$ | $-CF_3$ | $-N[(CH_2)_2CH_3]_2$ | S | 373 | |
| 23 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-(4-C_6H_4Cl)$ | S | 427 | |
| 24 | H | $-CF_3$ | $-CF_3$ | (4-methyl)piperidin-1-yl | S | 371 | |
| 25 | H | $-CF_3$ | $-CF_3$ | $-N[CH_2-CH(CH_3)_2]_2$ | S | 401 | |
| 26 | H | $-CF_3$ | $-CF_3$ | pyrrolidin-1-yl | S | 343 | |
| 27 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3$-(imidazol-1-yl) | S | 397 | |
| 28 | H | $-CF_3$ | $-CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | S | 405 | |
| 29 | H | $-CF_3$ | $-CF_3$ | (2,6-dimethyl)morpholin-4-yl | S | 387 | |
| 30 | H | $-CF_3$ | $-CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S | 502 | |
| 31 | H | $-CF_3$ | $-CF_3$ | azepin-1-yl | S | 371 | |
| 32 | H | $-CF_3$ | $-CF_3$ | (4-benzoyl)piperidin-1-yl | S | 461 | |
| 33 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3$-Ph | S | 407 | |
| 34 | H | $-CF_3$ | $-CF_3$ | -NH-(4-hydroxycyclohexyl) | S | 387 | |
| 35 | H | $-CF_3$ | $-CF_3$ | -NH-(3-hydroxycyclohexyl) | S | 387 | |
| 36 | H | $-CF_3$ | $-CF_3$ | 4-hydroxypiperidin-1-yl | S | 373 | |
| 37 | H | $-CF_3$ | $-CF_3$ | 3-hydroxypiperidin-1-yl | S | 373 | |
| 38 | H | $-CF_3$ | $-CF_3$ | 3-hydroxypyrrolidin-1-yl | S | 359 | |
| 39 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-OH$ | S | 333 | |
| 40 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-OH$ | S | 347 | |
| 41 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_4-OH$ | S | 361 | |
| 42 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_6-OH$ | S | 389 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 43 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-$(morpholin-4-yl) | S | 402 | |
| 44 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-$(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S | 443 | |
| 45 | H | $-CF_3$ | $-CF_3$ | (4-acetyl)piperazin-1-yl | S | 400 | |
| 46 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-(2-C_6H_4Cl)$ | S | 413 | |
| 47 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | S | 361 | |
| 48 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | S | 345 | |
| 49 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | S | 361 | 361 |
| 50 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-$(cyclohexyl) | S | 385 | |
| 51 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-$(4-pyridyl) | S | 394 | |
| 52 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-CH_2-$(4-pyridyl) | S | 408 | 408 |
| 53 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-NH-$(2-pyridyl) | S | 423 | 423 |
| 54 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-$(2-pyridyl) | S | 394 | |
| 55 | H | $-CF_3$ | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S | 483 | 483 |
| 56 | H | $-CF_3$ | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S | 469 | |
| 57 | H | $-CF_3$ | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | S | 452 | |
| 58 | H | $-CF_3$ | $-CF_3$ | $-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$ | S | 449 | |
| 59 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | S | 439 | 439 |
| 60 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_2-OH)-Ph$ | S | 409 | |
| 61 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)-Ph$ | S | 423 | 423 |
| 62 | H | $-CF_3$ | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | S | 462 | |
| 63 | H | $-CF_3$ | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S | 615 | 615 |
| 64 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S | 538 | |
| 65 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-$(3-pyridyl) | S | 380 | |
| 66 | H | -Cl | -Cl | $-NH-(CH_2)_2-CH(CH_3)_2$ | S | 292 | |
| 67 | H | -Cl | -Cl | $-NH-CH(CH_3)_2$ | S | 264 | |
| 68 | H | -Cl | -Cl | $-NH-CH_2-CH(CH_3)_2$ | S | 278 | |
| 69 | H | -Cl | -Cl | $-NH-CH_2-C(CH_3)_3$ | S | 292 | 291 |
| 70 | H | -Cl | -Cl | $-NH-CH_2-CF_3$ | S | 304 | |
| 71 | H | -Cl | -Cl | $-NH-CH_2-CCH$ | S | 260 | |
| 72 | H | -Cl | -Cl | $-N[(CH_2)_2CH_3]_2$ | S | 306 | |
| 73 | H | -Cl | -Cl | $-NH-(CH_2)_2-(4-C_6H_4Cl)$ | S | 360 | |
| 74 | H | -Cl | -Cl | (4-methyl)piperidin-1-yl | S | 304 | |
| 75 | H | -Cl | -Cl | $-N[CH_2-CH(CH_3)_2]_2$ | S | 334 | |
| 76 | H | -Cl | -Cl | pyrrolidin-1-yl | S | 276 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 77 | H | -Cl | -Cl | -NH-$(CH_2)_3$-(imidazol-1-yl) | S | 330 |
| 78 | H | -Cl | -Cl | 1,2,3,4-tetrahydroisoquinolin-2-yl | S | 338 |
| 79 | H | -Cl | -Cl | (2,6-dimethyl)morpholin-4-yl | S | 320 |
| 80 | H | -Cl | -Cl | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S | 435 |
| 81 | H | -Cl | -Cl | azepin-1-yl | S | 304 |
| 82 | H | -Cl | -Cl | (4-benzoyl)piperidin-1-yl | S | 394 |
| 83 | H | -Cl | -Cl | -NH-$(CH_2)_3$-Ph | S | 340 |
| 84 | H | -Cl | -Cl | -NH-(4-hydroxycyclohexyl) | S | 320 |
| 85 | H | -Cl | -Cl | -NH-(3-hydroxycyclohexyl) | S | 320 |
| 86 | H | -Cl | -Cl | 4-hydroxypiperidin-1-yl | S | 306 |
| 87 | H | -Cl | -Cl | 3-hydroxypiperidin-1-yl | S | 306 |
| 88 | H | -Cl | -Cl | 3-hydroxypyrrolidin-1-yl | S | 292 |
| 89 | H | -Cl | -Cl | -NH-$(CH_2)_2$-OH | S | 266 |
| 90 | H | -Cl | -Cl | -NH-$(CH_2)_3$-OH | S | 280 |
| 91 | H | -Cl | -Cl | -NH-$(CH_2)_4$-OH | S | 294 |
| 92 | H | -Cl | -Cl | -NH-$(CH_2)_6$-OH | S | 322 |
| 93 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(morpholin-4-yl) | S | 335 |
| 94 | H | -Cl | -Cl | -NH-$CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S | 376 |
| 95 | H | -Cl | -Cl | (4-acetyl)piperazin-1-yl | S | 333 |
| 96 | H | -Cl | -Cl | -NH-$CH_2$-(2-$C_6H_4Cl$) | S | 346 |
| 97 | H | -Cl | -Cl | -N(Et)-$(CH_2)_2$-OH | S | 294 |
| 98 | H | -Cl | -Cl | -NH-$(CH_2)_3$-$CH_3$ | S | 278 |
| 99 | H | -Cl | -Cl | -NH-$C(CH_3)_2$-$CH_2$-OH | S | 294 |
| 100 | H | -Cl | -Cl | -NH-$CH_2$-(cyclohexyl) | S | 318 |
| 101 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(4-pyridyl) | S | 327 |
| 102 | H | -Cl | -Cl | -N(Et)-$CH_2$-(4-pyridyl) | S | 341 |
| 103 | H | -Cl | -Cl | -NH-$(CH_2)_3$-NH-(2-pyridyl) | S | 356 |
| 104 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(2-pyridyl) | S | 327 |
| 105 | H | -Cl | -Cl | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S | 416 |
| 106 | H | -Cl | -Cl | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S | 402 |
| 107 | H | -Cl | -Cl | 4-(2-furoyl)piperazin-1-yl | S | 385 |
| 108 | H | -Cl | -Cl | -NH-CH(cyclopropyl)(4-$C_6H_4$-$OCH_3$) | S | 382 |
| 109 | H | -Cl | -Cl | -N($CH_3$)-$CH_2$-CH(OH)-(4-$C_6H_4$-OH) | S | 372 |
| 110 | H | -Cl | -Cl | -NH-CH($CH_2$-OH)-Ph | S | 342 |
| 111 | H | -Cl | -Cl | -NH-CH($CH_3$)-CH(OH)-Ph | S | 356 |
| 112 | H | -Cl | -Cl | -NH-(1-benzylpiperidin-4-yl) | S | 395 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 113 | H | -Cl | -Cl | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S | 548 | |
| 114 | H | -Cl | -Cl | -N($CH_3$)-($CH_2$)$_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S | 471 | |
| 115 | H | -Cl | -Cl | -NH-$CH_2$-(3-pyridyl) | S | 313 | |
| 116 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-$CH(CH_3)_2$ | O | 343 | |
| 117 | H | -$CF_3$ | -$CF_3$ | -NH-$CH(CH_3)_2$ | O | 315 | |
| 118 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-$CH(CH_3)_2$ | O | 329 | |
| 119 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-$C(CH_3)_3$ | O | 343 | 343 |
| 120 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-$CF_3$ | O | 355 | 355 |
| 121 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-CCH | O | 311 | |
| 122 | H | -$CF_3$ | -$CF_3$ | -N[($CH_2$)$_2$$CH_3$]$_2$ | O | 357 | |
| 123 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-(4-$C_6H_4Cl$) | O | 411 | |
| 124 | H | -$CF_3$ | -$CF_3$ | (4-methyl)piperidin-1-yl | O | 355 | |
| 125 | H | -$CF_3$ | -$CF_3$ | -N[$CH_2$-$CH(CH_3)_2$]$_2$ | O | 385 | |
| 126 | H | -$CF_3$ | -$CF_3$ | pyrrolidin-1-yl | O | 327 | |
| 127 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-(imidazol-1-yl) | O | 381 | |
| 128 | H | -$CF_3$ | -$CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | O | 389 | |
| 129 | H | -$CF_3$ | -$CF_3$ | (2,6-dimethyl)morpholin-4-yl | O | 371 | |
| 130 | H | -$CF_3$ | -$CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | O | 486 | |
| 131 | H | -$CF_3$ | -$CF_3$ | azepin-1-yl | O | 355 | |
| 132 | H | -$CF_3$ | -$CF_3$ | (4-benzoyl)piperidin-1-yl | O | 445 | |
| 133 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-Ph | O | 391 | |
| 134 | H | -$CF_3$ | -$CF_3$ | -NH-(4-hydroxycyclohexyl) | O | 371 | 371 |
| 135 | H | -$CF_3$ | -$CF_3$ | -NH-(3-hydroxycyclohexyl) | O | 371 | |
| 136 | H | -$CF_3$ | -$CF_3$ | 4-hydroxypiperidin-1-yl | O | 357 | |
| 137 | H | -$CF_3$ | -$CF_3$ | 3-hydroxypiperidin-1-yl | O | 357 | |
| 138 | H | -$CF_3$ | -$CF_3$ | 3-hydroxypyrrolidin-1-yl | O | 343 | 343 |
| 139 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-OH | O | 317 | |
| 140 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-OH | O | 331 | 331 |
| 141 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_4$-OH | O | 345 | |
| 142 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_6$-OH | O | 373 | |
| 143 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-(morpholin-4-yl) | O | 386 | |
| 144 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | O | 427 | |
| 145 | H | -$CF_3$ | -$CF_3$ | (4-acetyl)piperazin-1-yl | O | 384 | |
| 146 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-(2-$C_6H_4Cl$) | O | 397 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 147 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | O | 345 | |
| 148 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | O | 329 | |
| 149 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | O | 345 | |
| 150 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(cyclohexyl) | O | 369 | |
| 151 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(4-pyridyl) | O | 378 | |
| 152 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-CH_2$-(4-pyridyl) | O | 392 | |
| 153 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-NH$-(2-pyridyl) | O | 407 | |
| 154 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(2-pyridyl) | O | 378 | |
| 155 | H | $-CF_3$ | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | O | 467 | |
| 156 | H | $-CF_3$ | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | O | 453 | |
| 157 | H | $-CF_3$ | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | O | 436 | |
| 158 | H | $-CF_3$ | $-CF_3$ | $-NH-CH$(cyclopropyl)(4-$C_6H_4-OCH_3$) | O | 433 | 433 |
| 159 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | O | 423 | |
| 160 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_2-OH)-Ph$ | O | 393 | |
| 161 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)-Ph$ | O | 407 | |
| 162 | H | $-CF_3$ | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | O | 446 | |
| 163 | H | $-CF_3$ | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | O | 599 | |
| 164 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | O | 522 | |
| 165 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(3-pyridyl) | O | 364 | |
| 166 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-CH(CH_3)_2$ | S | 325 | |
| 167 | -Cl | H | $-CF_3$ | $-NH-CH(CH_3)_2$ | S | 297 | |
| 168 | -Cl | H | $-CF_3$ | $-NH-CH_2-CH(CH_3)_2$ | S | 311 | |
| 169 | -Cl | H | $-CF_3$ | $-NH-CH_2-C(CH_3)_3$ | S | 325 | 325 |
| 170 | -Cl | H | $-CF_3$ | $-NH-CH_2-CF_3$ | S | 337 | |
| 171 | -Cl | H | $-CF_3$ | $-NH-CH_2-CCH$ | S | 293 | |
| 172 | -Cl | H | $-CF_3$ | $-N[(CH_2)_2CH_3]_2$ | S | 339 | 339 |
| 173 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2$-(4-$C_6H_4Cl$) | S | 394 | |
| 174 | -Cl | H | $-CF_3$ | (4-methyl)piperidin-1-yl | S | 337 | 337 |
| 175 | -Cl | H | $-CF_3$ | $-N[CH_2-CH(CH_3)_2]_2$ | S | 367 | |
| 176 | -Cl | H | $-CF_3$ | pyrrolidin-1-yl | S | 309 | |
| 177 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3$-(imidazol-1-yl) | S | 363 | |
| 178 | -Cl | H | $-CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | S | 371 | |
| 179 | -Cl | H | $-CF_3$ | (2,6-dimethyl)morpholin-4-yl | S | 353 | |
| 180 | -Cl | H | $-CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S | 468 | |
| 181 | -Cl | H | $-CF_3$ | azepin-1-yl | S | 337 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 182 | -Cl | H | $-CF_3$ | (4-benzoyl)piperidin-1-yl | S | 427 | |
| 183 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-Ph$ | S | 373 | |
| 184 | -Cl | H | $-CF_3$ | -NH-(4-hydroxycyclohexyl) | S | 353 | |
| 185 | -Cl | H | $-CF_3$ | -NH-(3-hydroxycyclohexyl) | S | 353 | |
| 186 | -Cl | H | $-CF_3$ | 4-hydroxypiperidin-1-yl | S | 339 | |
| 187 | -Cl | H | $-CF_3$ | 3-hydroxypiperidin-1-yl | S | 339 | |
| 188 | -Cl | H | $-CF_3$ | 3-hydroxypyrrolidin-1-yl | S | 325 | |
| 189 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-OH$ | S | 299 | |
| 190 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-OH$ | S | 313 | |
| 191 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_4-OH$ | S | 327 | |
| 192 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_6-OH$ | S | 355 | |
| 193 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(morpholin-4-yl) | S | 368 | |
| 194 | -Cl | H | $-CF_3$ | $-NH-CH_2-$(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S | 409 | |
| 195 | -Cl | H | $-CF_3$ | (4-acetyl)piperazin-1-yl | S | 366 | |
| 196 | -Cl | H | $-CF_3$ | $-NH-CH_2-(2-C_6H_4Cl)$ | S | 380 | |
| 197 | -Cl | H | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | S | 327 | |
| 198 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | S | 311 | |
| 199 | -Cl | H | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | S | 327 | |
| 200 | -Cl | H | $-CF_3$ | $-NH-CH_2-$(cyclohexyl) | S | 351 | |
| 201 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(4-pyridyl) | S | 360 | |
| 202 | -Cl | H | $-CF_3$ | $-N(Et)-CH_2-$(4-pyridyl) | S | 374 | |
| 203 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-NH-$(2-pyridyl) | S | 389 | 388 |
| 204 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(2-pyridyl) | S | 360 | |
| 205 | -Cl | H | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S | 449 | |
| 206 | -Cl | H | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S | 435 | |
| 207 | -Cl | H | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | S | 418 | |
| 208 | -Cl | H | $-CF_3$ | $-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$ | S | 415 | |
| 209 | -Cl | H | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | S | 405 | |
| 210 | -Cl | H | $-CF_3$ | $-NH-CH(CH_2-OH)-Ph$ | S | 375 | 375 |
| 211 | -Cl | H | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)-Ph$ | S | 389 | |
| 212 | -Cl | H | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | S | 428 | |
| 213 | -Cl | H | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S | 582 | |
| 214 | -Cl | H | $-CF_3$ | $-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S | 505 | |
| 215 | -Cl | H | $-CF_3$ | $-NH-CH_2-$(3-pyridyl) | S | 346 | 346 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 216 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-(2,4-C_6H_3Cl_2)$ | O | 432 | 432 |

*Example 4. General synthetic pathway to 1-aryl-3-alkylthioureas*

A solution of the appropriately substituted aniline (8 mmol) and thiocarbonyldiimidazole (1.43 g ; 8 mmol) in dioxane (30 mL) was heated at 50°C for 48-72 h (until disappearance of the aniline from the reaction mixture monitored by TLC). The appropriate alkylamine (or cycloalkylalkylamine) (8 mmol) was added to the reaction medium and the resulting solution was heated at 60°C for 4-12 h. The solvent was removed by distillation under reduced pressure and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed with 4N HCl (50 mL), then with water (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the filtrate was concentrated to dryness. The residue was dissolved in a small volume of ethanol (5-10 mL). The solution was supplemented with 2N HCl (100 mL) and the resulting precipitate was collected by filtration, washed with water and dried (yields : 20-60%).

The following compounds have been obtained :

1-Cyclohexylmethyl-3-(3,5-dichlorophenyl)thiourea
mp 134-135°C. IR (KBr) : 3261, 3079, 2922, 2850, 1552, 1445, 1337, 1248 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{18}Cl_2N_2S$ (317.28) : C, 53.00 ; H, 5.72 ; N, 8.83 ; S, 10.11. Found : C, 53.13 ; H, 6.10 ; N, 9.00 ; S, 10.38.

1-Cyclohexylmethyl-3-(3,5-difluorophenyl)thiourea
mp 125-127°C. IR (KBr) : 3318, 3201, 2924, 2854, 1626, 1611, 1565, 1536, 1477, 1262, 1252, 1122 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{18}F_2N_2S$ (284.37) : C, 59.13 ; H, 6.38 ; N, 9.85 ; S, 11.28. Found : C, 59.33 ; H, 6.49 ; N, 10.22 ; S, 11.01.

1-Cyclohexylmethyl-3-(2,5-difluorophenyl)thiourea

mp 89-91°C. IR (KBr) : 3316, 3168, 2922, 2850, 1553, 1500, 1250, 1212, 1196, 1184 $cm^{-1}$. Anal. Calcd. for $C_{14}H_{18}F_2N_2S$ (284.37) : C, 59.13 ; H, 6.38 ; N, 9.85 ; S, 11.28. Found : C, 59.20 ; H, 6.63 ; N, 10.22 ; S, 11.33.

(R)-1-(1-Cyclohexylethyl)-3-(3,5-difluorophenyl)thiourea
mp 121-123°C. IR (KBr) : 3315, 3200, 3043, 2924, 2852, 1625, 1612, 1570, 1525, 1477, 1254, 1120 $cm^{-1}$. Anal. Calcd. for $C_{15}H_{20}F_2N_2S$ (298.40) : C, 60.38 ; H, 6.75 ; N, 9.39 ; S, 10.75. Found : C, 60.23 ; H, 6.92 ; N, 9.46 ; S, 11.05.

*Example 5 Heptanoic acid (3,5-bis(trifluoromethyl)phenyl)amide*

To a solution of heptanoyl chloride (0.186 ml, 1.1 mmol) in diethyl ether (1 ml) 3,5-bis-(trifluoromethyl)aniline (0.196 ml, 1.3 mmol) was added dropwise. After stirring for 2 h, the precipitate was filtered off and washed with diethyl ether. The filtrate was concentrated to give a sirup, which was purified by flash chromatography using ethyl acetate/heptane 1:4 and 1:2 to give the title compound as oily crystals. Yield 0.65 g (83%). The product could be recrystalised from ethanol/water to give oily crystals contaminated with heptanoic chloride (3.67 mol%). MA. Calculated for $C_{15}H_{17}NOF_6.0.1C_7H_{13}ClO$: C 53.22%; H 5.23%; N 3.95% Found: C 53.31%; H 5.10%; N 4.06%. EI SP/MS: 341 (M+ ). $^1$H-NMR (DMSO): δ 10.55 (s, 1H, NH); 8.27 (s, 2H); 7.70 (s, 1H); 2.35 (t, 2H); 1.60 (p, 2H); 1.3 (m, 6H); 0.88 ppm (t, 3H).

*Example 6 N-(3,5-Bis(trifluoromethyl)phenyl)-2-phenoxypropionamide*

To a solution of 2-phenoxypropionyl chloride (0.22 g, 1.1 mmol) in diethyl ether (4 ml) 3,5-bis-(trifluoromethyl)aniline (0.200 ml, 1.3 mmol) was added. After stirring for 2.5 h the reaction mixture was filtered and the filtrate concentrated to give a sirup, which was crystalised from toluene to give the title compound as white crystals. Yield 0.321 g (75%).mp 113.5-114.5°C. MA. Calculated for $C_{17}H_{13}NO_2F_6$: C 54.12%; H 3.47%; N 3.71% Found: C 54.21%; H 3.49%; N 3.68%. EI SP/MS: 377 (M+ ). $^1$H-NMR (DMSO): δ 10.80 (s, 1H, NH); 8.39 (s, 2H); 7.80 (s, 1H); 7.3 (m, 2H); 6.95 (m, 3H); 4.94 (q, 1H); 1.57 ppm (d, 3H).

*Example 7 1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)urea*

4-Chlorophenylisocyanate (0.175 ml, 1.36 mmol) was added to 3,5-bis-(trifluoromethyl)aniline (0.233 ml, 1.5 mmol) and stirred for 1 h. The almost solid reaction mixture was recrystalised first from ethyl acetate and then from toluene to give the title compound. Yield 0.315g (61%). Mp 224.5-225.0°C. EI SP/MS: 382 (M+).
1H-NMR (DMSO): δ 9.42 (br s, 1H, NH); 9.13 (br s, 1H, NH); 8.12 (s, 2H); 7.63 (s, 1H); 7.50 (d, 2H); 7.35 ppm (d, 2H).

*Example 8 N-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylacrylamide*

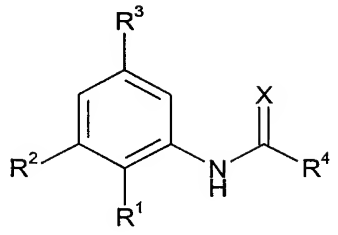
The title compound was prepared from 3,5-bis(trifluoromethyl)aniline and cinnamoyl chloride by a method analogous to the one described in Example 2; LC-MS: m/e 360 ($M^+$ +1).

*Example 9 2-Phenylcyclopropanecarboxylic acid (3,5-bis(trifluoromethyl)phenyl)-amide*

The title compound was prepared from 3,5-bis(trifluoromethyl)aniline and 2-phenylcyclopropanecarboxylic acid chloride by a method analogous to the one described in Example 2; LC-MS: m/e 374 ($M^+$ +1).

CLAIMS

1. A compound of the general formula I



I

wherein

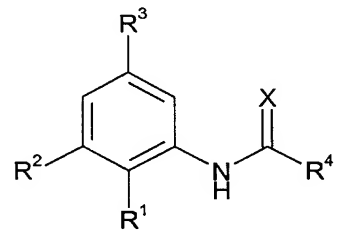
$R^1$ and $R^2$ are independently hydrogen, trifluoromethyl or halogen, with the provisio that $R^1$ and $R^2$ are not simultaneously hydrogen;

$R^3$ is trifluoromethyl or halogen;

$R^4$ is straight or branched alkyl optionally substituted with $C_{3-8}$-cycloalkyl, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl, or
$R^4$ is Y-$R^5$, Y being -O- or -N($R^6$)- and $R^5$ and $R^6$ being independently straight or branched alkyl optionally substituted with $C_{3-8}$-cycloalkyl, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl;
or $R^5$ and $R^6$ are linked to each other forming a 3-8 membered ring;

X is O or S;
or a pharmaceutically acceptable salts thereof.

2. A compound of the general formula I



I

wherein

$R^1$ is hydrogen, trifluoromethyl or halogen;

$R^2$ is hydrogen, trifluoromethyl or halogen;

$R^3$ is trifluoromethyl or halogen;

$R^4$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl or aryloxy; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or
Y-$R^5$, wherein Y is -O- or -N($R^6$)-
wherein $R^5$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or
aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;
$R^6$ is hydrogen; or
straight or branched alkyl optionally substituted with $C_{3-8}$-cycloalkyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

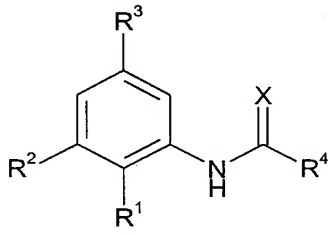
$R^5$ and $R^6$ are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl or pyrrolidinylcarbonylmethyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or
piperidinyl; or
$R^5$ and $R^6$ are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that $R^1$ and $R^2$ are not both hydrogen at the same time;

3. A compound of the general formula I



I

wherein

$R^1$ is hydrogen, trifluoromethyl or halogen;

$R^2$ is hydrogen, trifluoromethyl or halogen;

$R^3$ is trifluoromethyl or halogen;

$R^4$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl or aryloxy; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or
Y-$R^5$, wherein Y is -O- or -N($R^6$)-
wherein $R^5$ is straight or branched alkyl, $C_{2-6}$-alkenyl or $C_{2-6}$-alkynyl, optionally substituted with $C_{3-8}$-cycloalkyl, imidazolyl, methoxyphenyl or 10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl;
heterocyclyl, optionally substituted with halogen, cyano, benzyl or trifluoromethyl; or
aryloxy, optionally substituted with halogen, cyano or trifluoromethyl;

$R^6$ is hydrogen; or
straight or branched alkyl optionally substituted with $C_{3-8}$-cycloalkyl; or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
heterocyclyl, optionally substituted with halogen, cyano or trifluoromethyl; or
aryloxy optionally substituted with halogen, cyano or trifluoromethyl; or

$R^5$ and $R^6$ are linked to form a 3-8 membered ring which is optionally substituted with straight or branched alkyl, optionally substituted with pyrrolidinylcarbonylmethyl (??); or
aryl optionally substituted with halogen, cyano or trifluoromethyl; or
furoyl, benzoyl, acetyl, hydroxy, aminocarbonyl; or
piperidinyl; or
$R^5$ and $R^6$ are linked to form a saturated or unsaturated isoquinolin ring, optionally substituted with methoxy or dimethoxybenzyl;

X is O or S;

or a pharmaceutically acceptable salts thereof.

with the proviso that $R^1$ and $R^2$ are not both hydrogen at the same time;

and further provided that:

when $R^2$ is hydrogen and $R^1$ and $R^3$ are chloro, then
$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
$R^4$ can not be n-alkyl;
$R^4$ can not be $-(CH_2)_3$-OAr;
$R^4$ can not be 2,6-dimethylpiperidin-1-yl, methylamino, butylamino, benzylamino, arylamino, dimethylamino, diethylamino, dipropylamino, dibenzylamino, (methyl)(propargyl)amino, (1-phenylcyclohex-1-yl)methylamino, 4-heteroarylpiperazin-1-yl, (6-methylpyridin-2-yl)methylamino, (4-pyridinylmethyl)(methyl)amino or 2,5-dimethylpyrrolidin-1-yl;
and further provided that:

when $R^2$ is hydrogen and $R^1$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be methyl, pyridyl, ethyl, n-propyl or 2-propylbutyl;
and further provided that:

when $R^1$ is hydrogen and $R^2$ and $R^3$ are chloro, then
$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with aryl, aryloxy, alkylamino, arylamino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium or aminoalkyl;
$R^4$ can not be n-alkyl, cyclopropyl or 2-propylbutyl;
$R^4$ can not be $-(CH_2)_3$-OAr or $-CH(OH)CH_3$;
$R^4$ can not be arylamino, methylamino, isobutylamino, butylamino, 3-hydroxypropylamino, dimethylamino, [1-methyl-1-(4-bromophenyl)ethyl]amino, (methyl)(propargyl)amino, (isopropyl)(propargyl)amino, di(n-butyl)amino, dibenzylamino or (benzyl)(n-butyl)amino;
and further provided that:

when X is oxygen, $R^1$ is hydrogen and $R^2$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be heterocyclyl;
$R^4$ can not be methyl, unsubstituted or monosubstituted with heteroaryloxy, ammonium, acyl, 1-oximoalkyl, heterocyclyl or 1-iminoalkyl;
$R^4$ can not be 2-propylbutyl or cyclopropyl;
$R^4$ can not be benzylamino, 2-phenylethylamino, (1-phenyl)ethylamino, 4-chlorobenzylamino, 2-chlorobenzylamino, 2-(4-chlorophenyl)ethylamino, 3,4-dichlorobenzylamino, (3,4-dichlorobenzyl)(methyl)amino, (2-ethylhex-1-yl)amino, isopropylamino, propylamino, butylamino or 4-methyl-1-piperazinyl;
and further provided that:

when X is sulfur, $R^1$ is hydrogen and $R^2$ and $R^3$ are trifluoromethyl, then
$R^4$ can not be benzylamino, 3,4-dimethylbenzylamino, 4-methoxybenzylamino, 3,4-dichlorobenzylamino, (2-hydroxy-1-methyl-2-phenylethyl)(methyl)amino, isopropylamino, n-propylamino, n-pentylamino, 4-chlorobenzylamino, 1-piperidinyl, 4-morpholinyl, 4-methyl-1-piperazinyl, 2,6-dimethyl-4-thiomorpholinyl, 4-(2-hydroxyethyl)piperazin-1-yl, 4-phenylpiperazin-1-yl, 4-benzylpiperazin-1-yl or 4-ethoxycarbonylpiperazin-1-yl;

and further provided that:

when $R^1$ is chloro, $R^2$ is hydrogen and $R^3$ is trifluoromethyl, then
$R^4$ can not be substituted or unsubstituted aryl or heteroaryl or heterocyclyl;
$R^4$ can not be methyl, unsubstituted or substituted with aryl, heteroaryl, aryloxy, amino, halogen, heterocyclyl, acyl, 1-iminoalkyl, 1-iminoaryl, aminocarbonyl, 1-hydrazinoalkyl, 1-hydrazinoaryl, alkylthio, arylthio, heterocyclylthio, ammonium, aminoalkyl;
$R^4$ can not be unsubstituted n-alkyl, cyclopropyl, isopropyl, isobutyl, benzyl, 2-ethylpropyl, 2-propylbutyl;
$R^4$ can not be diisopropylamino, 2,6-dimethylpiperidin-1-yl, methylamino, dimethylamino, (1,1-dimethylpropargyl)amino, ethylamino, butylamino, (2-hydroxyprop-1-yl)amino or 1-adamantylamino.

4. A compound according to claim1, 2 or 3, wherein $R^1$ is hydrogen and $R^2$ and $R^3$ are trifluoromethyl.

5. A compound according to claim 1, 2 or 3, wherein $R^1$ is hydrogen and $R^2$ and $R^3$ are chloro.

6. A compound according to claim 1, 2 or 3, wherein $R^1$ is hydrogen and $R^2$ and $R^3$ are fluoro.

7. A compound according to claim 1, 2 or 3, wherein $R^2$ is hydrogen and $R^1$ and $R^3$ are fluoro.

8. A compound according to claim 1, 2 or 3, wherein $R^2$ is hydrogen, $R^1$ is chloro and $R^3$ is trifluoromethyl.

9. A compound according to any of the preceding claims, wherein X = O and $R^4$ = -NH-$R^5$, $R^5$ being lower straight or branched alkyl, optionally substituted with $C_{3-8}$-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

10. A compound according to any of the preceding claims, wherein X = S and $R^4$ = -NH-$R^5$, $R^5$ being lower straight or branched alkyl, optionally substituted with $C_{3-8}$-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

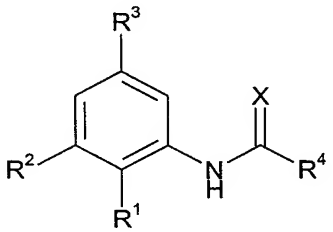
11. A compound according to any of the preceding claims, wherein X = O and $R^4$ is lower straight or branched alkyl, optionally substituted with $C_{3-8}$-cycloalkyl, halogen, hydroxy, heterocyclyl, aryloxy, and aryl optionally substituted with halogen or trifluoromethyl.

12. A compound according to claim wherein X is S and $R^4$ is N-$R^5$ wherein $R^5$ is alkyl substituted with cyclohexyl.

13. A compound according to claim 4 wherein X is O and $R^4$ is alkyl, phenyl substituted with chloro or O-$R^5$, wherein $R^5$ is phenyl.

14. A compound selected from the group consisting of
1-[3,5-Bis-(trifluoromethyl)phenyl]-3-(2,4-dichlorobenzyl)urea
1-Cyclohexylmethyl-3-(3,5-dichlorophenyl)thiourea
1-Cyclohexylmethyl-3-(3,5-difluorophenyl)thiourea
1-Cyclohexylmethyl-3-(2,5-difluorophenyl)thiourea
(R)-1-(1-Cyclohexylethyl)-3-(3,5-difluorophenyl)thiourea
Heptanoic acid (3,5-bis(trifluoromethyl)phenyl)amide
N-(3,5-Bis(trifluoromethyl)phenyl)-2-phenoxypropionamide
1-(3,5-Bis(trifluoromethyl)phenyl)-3-(4-chlorophenyl)urea
N-(3,5-Bis(trifluoromethyl)phenyl)-3-phenylacrylamide or
2-Phenylcyclopropanecarboxylic acid (3,5-bis(trifluoromethyl)phenyl)-amide.

15. A compound of formula I selected from the group consisting of:



I

| No | $R^1$ | $R^2$ | $R^3$ | $R^4$ | X |
|---|---|---|---|---|---|
| 1 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2CH_3$ | O |
| 2 | H | $-CF_3$ | $-CF_3$ | -NH-(cyclohexyl) | O |
| 3 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_3$ | O |
| 4 | H | $-CF_3$ | $-CF_3$ | $-NH-(4-C_6H_4Cl)$ | O |
| 5 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)_2$ | O |
| 6 | H | $-CF_3$ | $-CF_3$ | $-(3-C_6H_4CN)$ | O |
| 7 | H | $-CF_3$ | $-CF_3$ | $-CH(O-Ph)CH_3$ | O |
| 8 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2CH_3$ | O |
| 9 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_5CH_3$ | O |
| 10 | H | $-CF_3$ | $-CF_3$ | $-C(CH_3)_3$ | O |
| 11 | H | $-CF_3$ | $-CF_3$ | cyclopropyl | O |
| 12 | H | $-CF_3$ | $-CF_3$ | $-CH(CH_3)_2$ | O |
| 13 | H | $-CF_3$ | $-CF_3$ | -CH(Et)(n-butyl) | O |
| 14 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2$-(cyclopentyl) | O |
| 15 | H | $-CF_3$ | $-CF_3$ | $-(CH_2)_2$-Ph | O |
| 16 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-CH(CH_3)_2$ | S |
| 17 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)_2$ | S |
| 18 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CH(CH_3)_2$ | S |
| 19 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-C(CH_3)_3$ | S |
| 20 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CF_3$ | S |
| 21 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-CCH$ | S |
| 22 | H | $-CF_3$ | $-CF_3$ | $-N[(CH_2)_2CH_3]_2$ | S |
| 23 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-(4-C_6H_4Cl)$ | S |
| 24 | H | $-CF_3$ | $-CF_3$ | (4-methyl)piperidin-1-yl | S |
| 25 | H | $-CF_3$ | $-CF_3$ | $-N[CH_2-CH(CH_3)_2]_2$ | S |
| 26 | H | $-CF_3$ | $-CF_3$ | pyrrolidin-1-yl | S |
| 27 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3$-(imidazol-1-yl) | S |
| 28 | H | $-CF_3$ | $-CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | S |
| 29 | H | $-CF_3$ | $-CF_3$ | (2,6-dimethyl)morpholin-4-yl | S |
| 30 | H | $-CF_3$ | $-CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S |
| 31 | H | $-CF_3$ | $-CF_3$ | azepin-1-yl | S |
| 32 | H | $-CF_3$ | $-CF_3$ | (4-benzoyl)piperidin-1-yl | S |
| 33 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3$-Ph | S |

| | | | | | |
|---|---|---|---|---|---|
| 34 | H | $-CF_3$ | $-CF_3$ | -NH-(4-hydroxycyclohexyl) | S |
| 35 | H | $-CF_3$ | $-CF_3$ | -NH-(3-hydroxycyclohexyl) | S |
| 36 | H | $-CF_3$ | $-CF_3$ | 4-hydroxypiperidin-1-yl | S |
| 37 | H | $-CF_3$ | $-CF_3$ | 3-hydroxypiperidin-1-yl | S |
| 38 | H | $-CF_3$ | $-CF_3$ | 3-hydroxypyrrolidin-1-yl | S |
| 39 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2-OH$ | S |
| 40 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-OH$ | S |
| 41 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_4-OH$ | S |
| 42 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_6-OH$ | S |
| 43 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(morpholin-4-yl) | S |
| 44 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S |
| 45 | H | $-CF_3$ | $-CF_3$ | (4-acetyl)piperazin-1-yl | S |
| 46 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-(2-C_6H_4Cl)$ | S |
| 47 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | S |
| 48 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | S |
| 49 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | S |
| 50 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(cyclohexyl) | S |
| 51 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(4-pyridyl) | S |
| 52 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-CH_2$-(4-pyridyl) | S |
| 53 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-NH$-(2-pyridyl) | S |
| 54 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(2-pyridyl) | S |
| 55 | H | $-CF_3$ | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S |
| 56 | H | $-CF_3$ | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S |
| 57 | H | $-CF_3$ | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | S |
| 58 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(cyclopropyl)(4-C_6H_4-OCH_3)$ | S |
| 59 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | S |
| 60 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_2-OH)$-Ph | S |
| 61 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)$-Ph | S |
| 62 | H | $-CF_3$ | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | S |
| 63 | H | $-CF_3$ | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S |
| 64 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S |
| 65 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(3-pyridyl) | S |
| 66 | H | -Cl | -Cl | $-NH-(CH_2)_2-CH(CH_3)_2$ | S |
| 67 | H | -Cl | -Cl | $-NH-CH(CH_3)_2$ | S |
| 68 | H | -Cl | -Cl | $-NH-CH_2-CH(CH_3)_2$ | S |
| 69 | H | -Cl | -Cl | $-NH-CH_2-C(CH_3)_3$ | S |

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|---|---|---|---|---|---|
| 70 | H | -Cl | -Cl | -NH-$CH_2$-$CF_3$ | S |
| 71 | H | -Cl | -Cl | -NH-$CH_2$-CCH | S |
| 72 | H | -Cl | -Cl | -N[$(CH_2)_2CH_3$]$_2$ | S |
| 73 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(4-$C_6H_4Cl$) | S |
| 74 | H | -Cl | -Cl | (4-methyl)piperidin-1-yl | S |
| 75 | H | -Cl | -Cl | -N[$CH_2$-$CH(CH_3)_2$]$_2$ | S |
| 76 | H | -Cl | -Cl | pyrrolidin-1-yl | S |
| 77 | H | -Cl | -Cl | -NH-$(CH_2)_3$-(imidazol-1-yl) | S |
| 78 | H | -Cl | -Cl | 1,2,3,4-tetrahydroisoquinolin-2-yl | S |
| 79 | H | -Cl | -Cl | (2,6-dimethyl)morpholin-4-yl | S |
| 80 | H | -Cl | -Cl | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S |
| 81 | H | -Cl | -Cl | azepin-1-yl | S |
| 82 | H | -Cl | -Cl | (4-benzoyl)piperidin-1-yl | S |
| 83 | H | -Cl | -Cl | -NH-$(CH_2)_3$-Ph | S |
| 84 | H | -Cl | -Cl | -NH-(4-hydroxycyclohexyl) | S |
| 85 | H | -Cl | -Cl | -NH-(3-hydroxycyclohexyl) | S |
| 86 | H | -Cl | -Cl | 4-hydroxypiperidin-1-yl | S |
| 87 | H | -Cl | -Cl | 3-hydroxypiperidin-1-yl | S |
| 88 | H | -Cl | -Cl | 3-hydroxypyrrolidin-1-yl | S |
| 89 | H | -Cl | -Cl | -NH-$(CH_2)_2$-OH | S |
| 90 | H | -Cl | -Cl | -NH-$(CH_2)_3$-OH | S |
| 91 | H | -Cl | -Cl | -NH-$(CH_2)_4$-OH | S |
| 92 | H | -Cl | -Cl | -NH-$(CH_2)_6$-OH | S |
| 93 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(morpholin-4-yl) | S |
| 94 | H | -Cl | -Cl | -NH-$CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S |
| 95 | H | -Cl | -Cl | (4-acetyl)piperazin-1-yl | S |
| 96 | H | -Cl | -Cl | -NH-$CH_2$-(2-$C_6H_4Cl$) | S |
| 97 | H | -Cl | -Cl | -N(Et)-$(CH_2)_2$-OH | S |
| 98 | H | -Cl | -Cl | -NH-$(CH_2)_3$-$CH_3$ | S |
| 99 | H | -Cl | -Cl | -NH-C$(CH_3)_2$-$CH_2$-OH | S |
| 100 | H | -Cl | -Cl | -NH-$CH_2$-(cyclohexyl) | S |
| 101 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(4-pyridyl) | S |
| 102 | H | -Cl | -Cl | -N(Et)-$CH_2$-(4-pyridyl) | S |
| 103 | H | -Cl | -Cl | -NH-$(CH_2)_3$-NH-(2-pyridyl) | S |
| 104 | H | -Cl | -Cl | -NH-$(CH_2)_2$-(2-pyridyl) | S |
| 105 | H | -Cl | -Cl | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S |
| 106 | H | -Cl | -Cl | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S |

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|---|---|---|---|---|---|
| 107 | H | -Cl | -Cl | 4-(2-furoyl)piperazin-1-yl | S |
| 108 | H | -Cl | -Cl | -NH-CH(cyclopropyl)(4-$C_6H_4$-$OCH_3$) | S |
| 109 | H | -Cl | -Cl | -N($CH_3$)-$CH_2$-CH(OH)-(4-$C_6H_4$-OH) | S |
| 110 | H | -Cl | -Cl | -NH-CH($CH_2$-OH)-Ph | S |
| 111 | H | -Cl | -Cl | -NH-CH($CH_3$)-CH(OH)-Ph | S |
| 112 | H | -Cl | -Cl | -NH-(1-benzylpiperidin-4-yl) | S |
| 113 | H | -Cl | -Cl | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S |
| 114 | H | -Cl | -Cl | -N($CH_3$)-($CH_2$)$_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S |
| 115 | H | -Cl | -Cl | -NH-$CH_2$-(3-pyridyl) | S |
| 116 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-CH($CH_3$)$_2$ | O |
| 117 | H | -$CF_3$ | -$CF_3$ | -NH-CH($CH_3$)$_2$ | O |
| 118 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-CH($CH_3$)$_2$ | O |
| 119 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-C($CH_3$)$_3$ | O |
| 120 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-$CF_3$ | O |
| 121 | H | -$CF_3$ | -$CF_3$ | -NH-$CH_2$-CCH | O |
| 122 | H | -$CF_3$ | -$CF_3$ | -N[($CH_2$)$_2$$CH_3$]$_2$ | O |
| 123 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-(4-$C_6H_4$Cl) | O |
| 124 | H | -$CF_3$ | -$CF_3$ | (4-methyl)piperidin-1-yl | O |
| 125 | H | -$CF_3$ | -$CF_3$ | -N[$CH_2$-CH($CH_3$)$_2$]$_2$ | O |
| 126 | H | -$CF_3$ | -$CF_3$ | pyrrolidin-1-yl | O |
| 127 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-(imidazol-1-yl) | O |
| 128 | H | -$CF_3$ | -$CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | O |
| 129 | H | -$CF_3$ | -$CF_3$ | (2,6-dimethyl)morpholin-4-yl | O |
| 130 | H | -$CF_3$ | -$CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | O |
| 131 | H | -$CF_3$ | -$CF_3$ | azepin-1-yl | O |
| 132 | H | -$CF_3$ | -$CF_3$ | (4-benzoyl)piperidin-1-yl | O |
| 133 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-Ph | O |
| 134 | H | -$CF_3$ | -$CF_3$ | -NH-(4-hydroxycyclohexyl) | O |
| 135 | H | -$CF_3$ | -$CF_3$ | -NH-(3-hydroxycyclohexyl) | O |
| 136 | H | -$CF_3$ | -$CF_3$ | 4-hydroxypiperidin-1-yl | O |
| 137 | H | -$CF_3$ | -$CF_3$ | 3-hydroxypiperidin-1-yl | O |
| 138 | H | -$CF_3$ | -$CF_3$ | 3-hydroxypyrrolidin-1-yl | O |
| 139 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_2$-OH | O |
| 140 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_3$-OH | O |
| 141 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_4$-OH | O |
| 142 | H | -$CF_3$ | -$CF_3$ | -NH-($CH_2$)$_6$-OH | O |

| | | | | | |
|---|---|---|---|---|---|
| 143 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(morpholin-4-yl) | O |
| 144 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | O |
| 145 | H | $-CF_3$ | $-CF_3$ | (4-acetyl)piperazin-1-yl | O |
| 146 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-(2-C_6H_4Cl)$ | O |
| 147 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | O |
| 148 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | O |
| 149 | H | $-CF_3$ | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | O |
| 150 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(cyclohexyl) | O |
| 151 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(4-pyridyl) | O |
| 152 | H | $-CF_3$ | $-CF_3$ | $-N(Et)-CH_2$-(4-pyridyl) | O |
| 153 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_3-NH$-(2-pyridyl) | O |
| 154 | H | $-CF_3$ | $-CF_3$ | $-NH-(CH_2)_2$-(2-pyridyl) | O |
| 155 | H | $-CF_3$ | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | O |
| 156 | H | $-CF_3$ | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | O |
| 157 | H | $-CF_3$ | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | O |
| 158 | H | $-CF_3$ | $-CF_3$ | $-NH-CH$(cyclopropyl)$(4-C_6H_4-OCH_3)$ | O |
| 159 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | O |
| 160 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_2-OH)$-Ph | O |
| 161 | H | $-CF_3$ | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)$-Ph | O |
| 162 | H | $-CF_3$ | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | O |
| 163 | H | $-CF_3$ | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | O |
| 164 | H | $-CF_3$ | $-CF_3$ | $-N(CH_3)-(CH_2)_3$-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | O |
| 165 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2$-(3-pyridyl) | O |
| 166 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-CH(CH_3)_2$ | S |
| 167 | -Cl | H | $-CF_3$ | $-NH-CH(CH_3)_2$ | S |
| 168 | -Cl | H | $-CF_3$ | $-NH-CH_2-CH(CH_3)_2$ | S |
| 169 | -Cl | H | $-CF_3$ | $-NH-CH_2-C(CH_3)_3$ | S |
| 170 | -Cl | H | $-CF_3$ | $-NH-CH_2-CF_3$ | S |
| 171 | -Cl | H | $-CF_3$ | $-NH-CH_2-CCH$ | S |
| 172 | -Cl | H | $-CF_3$ | $-N[(CH_2)_2CH_3]_2$ | S |
| 173 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-(4-C_6H_4Cl)$ | S |
| 174 | -Cl | H | $-CF_3$ | (4-methyl)piperidin-1-yl | S |
| 175 | -Cl | H | $-CF_3$ | $-N[CH_2-CH(CH_3)_2]_2$ | S |
| 176 | -Cl | H | $-CF_3$ | pyrrolidin-1-yl | S |
| 177 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3$-(imidazol-1-yl) | S |
| 178 | -Cl | H | $-CF_3$ | 1,2,3,4-tetrahydroisoquinolin-2-yl | S |

| | | | | | |
|---|---|---|---|---|---|
| 179 | -Cl | H | $-CF_3$ | (2,6-dimethyl)morpholin-4-yl | S |
| 180 | -Cl | H | $-CF_3$ | 4-[(3-trifluoromethyl)phenyl]piperazin-1-yl | S |
| 181 | -Cl | H | $-CF_3$ | azepin-1-yl | S |
| 182 | -Cl | H | $-CF_3$ | (4-benzoyl)piperidin-1-yl | S |
| 183 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-Ph$ | S |
| 184 | -Cl | H | $-CF_3$ | -NH-(4-hydroxycyclohexyl) | S |
| 185 | -Cl | H | $-CF_3$ | -NH-(3-hydroxycyclohexyl) | S |
| 186 | -Cl | H | $-CF_3$ | 4-hydroxypiperidin-1-yl | S |
| 187 | -Cl | H | $-CF_3$ | 3-hydroxypiperidin-1-yl | S |
| 188 | -Cl | H | $-CF_3$ | 3-hydroxypyrrolidin-1-yl | S |
| 189 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-OH$ | S |
| 190 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-OH$ | S |
| 191 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_4-OH$ | S |
| 192 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_6-OH$ | S |
| 193 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(morpholin-4-yl) | S |
| 194 | -Cl | H | $-CF_3$ | $-NH-CH_2-$(1,3,3-trimethyl-5-hydroxy-1-cyclohexyl | S |
| 195 | -Cl | H | $-CF_3$ | (4-acetyl)piperazin-1-yl | S |
| 196 | -Cl | H | $-CF_3$ | $-NH-CH_2-(2-C_6H_4Cl)$ | S |
| 197 | -Cl | H | $-CF_3$ | $-N(Et)-(CH_2)_2-OH$ | S |
| 198 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-CH_3$ | S |
| 199 | -Cl | H | $-CF_3$ | $-NH-C(CH_3)_2-CH_2-OH$ | S |
| 200 | -Cl | H | $-CF_3$ | $-NH-CH_2-$(cyclohexyl) | S |
| 201 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(4-pyridyl) | S |
| 202 | -Cl | H | $-CF_3$ | $-N(Et)-CH_2-$(4-pyridyl) | S |
| 203 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_3-NH-$(2-pyridyl) | S |
| 204 | -Cl | H | $-CF_3$ | $-NH-(CH_2)_2-$(2-pyridyl) | S |
| 205 | -Cl | H | $-CF_3$ | [4-(piperidin-1-yl)-4-aminocarbonyl]piperidin-1-yl | S |
| 206 | -Cl | H | $-CF_3$ | 4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl | S |
| 207 | -Cl | H | $-CF_3$ | 4-(2-furoyl)piperazin-1-yl | S |
| 208 | -Cl | H | $-CF_3$ | $-NH-CH($cyclopropyl$)(4-C_6H_4-OCH_3)$ | S |
| 209 | -Cl | H | $-CF_3$ | $-N(CH_3)-CH_2-CH(OH)-(4-C_6H_4-OH)$ | S |
| 210 | -Cl | H | $-CF_3$ | $-NH-CH(CH_2-OH)-Ph$ | S |
| 211 | -Cl | H | $-CF_3$ | $-NH-CH(CH_3)-CH(OH)-Ph$ | S |
| 212 | -Cl | H | $-CF_3$ | -NH-(1-benzylpiperidin-4-yl) | S |
| 213 | -Cl | H | $-CF_3$ | 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl | S |
| 214 | -Cl | H | $-CF_3$ | $-N(CH_3)-(CH_2)_3-$(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl) | S |

| | | | | | |
|---|---|---|---|---|---|
| 215 | -Cl | H | $-CF_3$ | $-NH-CH_2-(3\text{-pyridyl})$ | S |
| 216 | H | $-CF_3$ | $-CF_3$ | $-NH-CH_2-(2,4-C_6H_3Cl_2)$ | O |

and pharmaceutically acceptable salts thereof.

16. Compounds according to any one of the preceding claims which are active as potassium channel openers.

17. A pharmaceutical composition comprising a compound according to claim 1 or 2 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

18. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as diabetes comprising a compound according to claim 1 or 2 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

19. A pharmaceutical composition for use in the treatment of diseases of the endocrinological system such as diabetes comprising a compound according to any of the claims 1 - 15 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form together with one or more pharmaceutically acceptable carriers or diluents.

20. The pharmaceutical composition according to claim 17 to 19 in the form of an oral dosage unit or parenteral dosage unit.

21. A pharmaceutical composition according to claim 17 to 19 wherein said compound is administered as a dose in a range from about 0.05 mg to 1000 mg, preferably from about 0.1 mg to 500 mg and especially in the range from 50 mg to 200 mg per day.

22. A compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use.

23. A compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for therapeutical use in the treatment or prevention of diseases of the endocrinological system, such as diabetes.

24. The use of a compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form as a medicament.

25. The use of a compound according to any of the claims 1 - 15 for preparing a medicament.

26. The use of a compound according to any one of the claims 1 - 15 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric form for the preparation of a medicament for the treatment or prevention of diseases of the endocrinological system, such as diabetes.

27. A method of treating or preventing diseases of the endocrinological system, such as diabetes in a subject in need thereof comprising administering an effective amount of a compound according to any of the claims 1 - 15 to said subject.

28. A process for the manufacture of a medicament to be used in the treatment or prevention of diseases of the endocrinological system, such as diabetes which process comprising bringing a compound of formula I according to any of the claims 1 - 15 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

29. Any novel feature or combination of features as described herein.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00337

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07C 275/28, C07C 335/16, C07C 233/07, C07C 271/26, C07D 295/16, C07D 203/04, C07D 205/02, A61K 31/17, A61K 31/16, A61K 31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| P,X | WO 9745400 A1 (NEUROSEARCH A/S), 4 December 1997 (04.12.97) -- | 1-25,28,29 |
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| X | WO 9422807 A1 (NEUROSEARCH A/S), 13 October 1994 (13.10.94) -- | 1-29 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search
5 November 1998

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00337

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | STN International, File CA, Chemical abstracts, volume 70, no. 13, 31 March 1969, (Columbus, Ohio, US), Laboratoires J. et al: "Dipropylacetylaniline derivatives as analgesics", abstract no. 57467, & ZA 6706114 680222 | 1-25,28,29 |
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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00337

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| X | DE 1803084 A1 (CIBA AKTIENGESELLSCHAFT), 19 June 1969 (19.06.69), page 9, examples 3,4,6; the claims<br>--<br>-------- | 1-15 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 98/00337

**Box I** Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24,27
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 24,27 relate to methods of treatment of the human or animal body by surgery or by therapy. See PCT, Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [X] Claims Nos.: 1-29
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims are not clear and concise. See PCT, Article 6. The search has therefore been incomplete. The claims 1-15 also include a great number of known compounds. Therefore, the search report does not include all relevant prior art.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II** Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/DK 98/00337

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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Information on patent family members

International application No.
PCT/DK 98/00337

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